Management of the Treatment-Experienced Patient

VIROLOGIC AND IMMUNOLOGIC FAILURE (Updated January 10, 2011)

Panel's Recommendations:

- ***Assessing and managing an antiretroviral (ARV)-experienced patient experiencing failure of antiretroviral therapy (ART) is complex. Expert advice is critical and should be sought.***
- ***Evaluation of virologic failure should include an assessment of the severity of the patient's HIV disease, ART history, use of concomitant medications with consideration of adverse drug interactions with ARV agents, HIV RNA and CD4 T-cell count trends over time, and prior drug-resistance testing results.***
- ***Drug-resistance testing should be obtained while the patient is taking the failing ARV regimen or within 4 weeks of treatment discontinuation (AII).***
- ***The goal of treatment for ARV-experienced patients with drug resistance who are experiencing virologic failure is to re-establish virologic suppression (e.g., HIV RNA <48 copies/mL) (AI).***
- ***To design a new regimen, the patient's treatment history and past and current resistance test results should be used to identify at least two (preferably three) fully active agents to combine with an optimized background ARV regimen (AI). A fully active agent is one that is likely to have ARV activity on the basis of the patient's treatment history, drug-resistance testing, and/or a novel mechanism of action.***
- ***In general, adding a single, fully active ARV in a new regimen is <u>not</u> recommended because of the risk of rapid development of resistance (BII).***
- ***In patients with a high likelihood of clinical progression (e.g., CD4 count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits (CI).***
- ***For some highly ART-experienced patients, maximal virologic suppression is not possible. In this case, ART should be continued (AI) with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression.***
- ***Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 cell count and increases the risk of clinical progression. Therefore, this strategy is <u>not</u> recommended (AI).***
- ***In the setting of virologic suppression, there is no consensus on how to define or treat immunologic failure.***

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

Virologic Definitions

Virologic suppression: A confirmed HIV RNA level below the limit of assay detection (e.g., <48 copies/mL).

Virologic failure: The inability to achieve or maintain suppression of viral replication (to an HIV RNA level <200 copies/mL).

Incomplete virologic response: Two consecutive plasma HIV RNA levels >200 copies/mL after 24 weeks on an ARV regimen. Baseline HIV RNA may affect the time course of response, and some regimens will take longer than others to suppress HIV RNA levels.

Virologic rebound: Confirmed detectable HIV RNA (to >200 copies/mL) after virologic suppression.

Persistent low-level viremia: Confirmed detectable HIV RNA levels that are <1,000 copies/mL.

Virologic blip: After virologic suppression, an isolated detectable HIV RNA level that is followed by a return to virologic suppression.

Causes of Virologic Failure

Virologic failure in a patient can occur for multiple reasons. Data from older patient cohorts suggested that suboptimal adherence and drug intolerance/toxicity accounted for 28%–40% of virologic failure and regimen discontinuations *[1-2]*. More recent data suggest that most virologic failure on first-line regimens occurred due to either pre-existing (transmitted) drug resistance or suboptimal adherence *[3]*. Factors associated with virologic failure include:

- Patient characteristics
  - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used)
  - lower pretreatment or nadir CD4 T-cell count
  - prior AIDS diagnosis
  - comorbidities (e.g., active substance abuse, depression)
  - presence of drug-resistant virus, either transmitted or acquired
  - prior treatment failure
  - incomplete medication adherence and missed clinic appointments

- ARV regimen characteristics
  - drug side effects and toxicities
  - suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs)
  - food/fasting requirements
  - adverse drug-drug interactions with concomitant medications
  - suboptimal virologic potency
  - prescription errors

- Provider characteristics, such as experience in treating HIV disease

- Other or unknown reasons

Management of Patients with Virologic Failure

Assessment of Virologic Failure

If virologic failure is suspected or confirmed, a thorough work-up is indicated, addressing the following factors:
- change in HIV RNA and CD4 T-cell counts over time
- occurrence of HIV-related clinical events
- ARV treatment history
- results of prior resistance testing (if any)
- medication-taking behavior (including adherence to recommended drug doses, dosing frequency, and food/fasting requirements)
- tolerability of medications
- concomitant medications and supplements (with consideration for adverse drug-drug interactions)
- comorbidities (including substance abuse)

In many cases, the cause(s) of virologic failure will be identified. In some cases, no obvious cause(s) may be identified. It is important to distinguish among the reasons for virologic failure because the approaches to subsequent therapy differ. The following potential causes of virologic failure should be explored in depth.

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) (e.g., difficulties accessing or tolerating medications, depression, active substance abuse) and

simplify the regimen if possible (e.g., decrease pill count or dosing frequency). (See **Adherence**.)

- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects, keeping in mind that even minor side effects can impact adherence. Management strategies for intolerance in the absence of drug resistance may include:
  - using symptomatic treatment (e.g., antiemetics, antidiarrheals)
  - changing one ARV to another within the same drug class, if needed (e.g., change to tenofovir [TDF] or abacavir [ABC] for zidovudine [ZDV]-related toxicities; change to nevirapine [NVP] or etravirine [ETR] for efavirenz [EFV]-related toxicities) *[4-5]*
  - changing from one drug class to another (e.g., from a non-nucleoside reverse transcriptase inhibitor [NNRTI] to a protease inhibitor [PI], from enfuvirtide [T-20] to raltegravir [RAL]) if necessary and no prior drug resistance is suspected

- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult **Drug Interactions** section and tables for common interactions) and make appropriate substitutions for ARV agents and/or concomitant medications, if possible. Therapeutic drug monitoring (TDM) may be helpful if pharmacokinetic drug-drug interactions or impaired drug absorption leading to decreased ARV exposure is suspected. (See also **Exposure-Response Relationship and Therapeutic Drug Monitoring**.)

- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation if the plasma HIV RNA level is >500 copies/mL **(AII)**. (See **Drug-Resistance Testing**.) Evaluate the degree of drug resistance and consider the patient's prior treatment history and prior resistance test results. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account. Routine genotypic or phenotypic testing gives information relevant for selecting nucleoside reverse transcriptase inhibitors (NRTIs), NNRTIs, and PIs. Additional drug-resistance tests for patients experiencing failure on fusion inhibitors and/or integrase strand transfer inhibitors (INSTIs) and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

Changing ART

There is no consensus on the optimal time to change therapy for virologic failure. The goal of ART is to suppress HIV replication to a level where drug-resistance mutations do not emerge. However, the specific level of viral suppression needed to achieve durable virologic suppression remains unknown. Selection of drug resistance does not appear to occur in patients with persistent HIV RNA levels suppressed to <48 copies/mL *[6]*, although this remains controversial *[7]*.

The clinical implications of HIV RNA in the range of >48 to <200 copies/mL in a patient on ART are controversial. Unlike the case with higher levels of HIV RNA, most, if not all, circulating virus from individuals with this level of HIV RNA results from the release of HIV from long-lived latently infected cells and does not signify ongoing viral replication with the emergence of drug-resistant virus *[8]*. Although some studies have suggested that viremia at this low level predicts subsequent failure *[9]* and can be associated with the evolution of drug resistance *[10]*, a large retrospective analysis showed that using an HIV RNA threshold for virologic failure of <200 copies/mL had the same predictive value as using a threshold of <50 copies/mL *[11]*.

Newer technologies (e.g., Taqman assay) have made it possible to detect HIV RNA in more patients with low level viremia (<200 copies/mL) than was possible with previous assays. Use of these newer assays has resulted in more confirmatory viral load testing than may be necessary *[12-14]*.

Persistent HIV RNA levels >200 copies/mL often are associated with evidence of viral evolution and drug-resistance mutation accumulation *[15]*; this is particularly common when HIV RNA levels are >500 copies/mL *[16]*. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should therefore be considered as virologic failure.

Viremia “blips” (e.g., viral suppression followed by a detectable HIV RNA level and then subsequent return to undetectable levels) usually are not associated with subsequent virologic failure *[17]*.

Management of Virologic Failure

Once virologic failure is confirmed, generally the regimen should be changed as soon as possible to avoid progressive accumulation of resistance mutations *[18]*.

Ideally, a new ARV regimen should contain at least two, and preferably three, fully active drugs on the basis of drug treatment history, resistance testing, or new mechanistic class **(AI)** *[19-27]*. Some ARV drugs (e.g., NRTIs) may contribute partial ARV activity to a regimen, despite drug resistance *[28]*, while others (e.g., T-20, NNRTIs, RAL) likely do not provide partial activity *[28-30]*. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. In addition, archived drug-resistance mutations may not be detected by standard drug-resistance tests, emphasizing the importance of considering treatment history and prior drug-resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed.

Early studies of ART-experienced patients identified factors associated with better virologic responses to subsequent regimens *[31-32]*. These factors included lower HIV RNA level and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of ARV drugs, and using ritonavir (RTV)-boosted PIs in PI-experienced patients.

More recent clinical trials support the strategy of conducting reverse transcriptase (RT) and protease (PT) resistance testing (both genotype and phenotype) while an ART-experienced patient is taking a failing ARV regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting at least two and preferably three active drugs for the new treatment regimen *[20-21, 23-24, 33]*. Higher genotypic and/or phenotypic susceptibility scores (quantitative measures of drug activity) are associated with better virologic responses *[23-24]*. Patients who receive more active drugs have a better and more prolonged virologic response than those with fewer active drugs in the regimen. Active ARV drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI—ETR, the PIs—darunavir [DRV] and tipranavir [TPV]) and drugs with new mechanisms of action (the fusion inhibitor—T-20, the CCR5 antagonist—maraviroc [MVC] in patients with R5 but not X4 virus, and the INSTI—RAL). Drug-resistance tests for patients experiencing failure on fusion inhibitors (FIs) and/or INSTIs and viral tropism tests for patients experiencing failure on a CCR5 antagonist also are available. (See **Drug-Resistance Testing**.)

Clinical Scenarios of Virologic Failure

- ***Low-level viremia (HIV RNA <1,000 copies/mL).*** Assess adherence. Consider variability in HIV RNA assays. Patients with HIV RNA <48 copies/mL or isolated increases in HIV RNA (“blips”) do not require a change in treatment *[13]* **(AII)**. There is no consensus regarding how to manage patients with HIV RNA levels >48 copies/mL and <200 copies/mL; HIV RNA levels should be followed over time to assess the need for changes (**AIII**). Patients with persistent HIV RNA levels >200 copies/mL often select out drug-resistant viral variants, particularly when HIV RNA levels are >500 copies/mL. Persistent plasma HIV RNA levels in the 200 to 1,000 copies/mL range should be considered as possible virologic failure; resistance testing should be attempted if the HIV RNA level is >500 copies/mL. For individuals with sufficient therapeutic options, consider treatment change **(BIII)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and NO drug resistance identified.*** Consider the timing of the drug-resistance test (e.g., was the patient off ARV for >4 weeks and/or nonadherent?). Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**.

- ***Repeated detectable viremia (HIV RNA >1,000 copies/mL) and drug resistance identified.*** The goals in this situation are to resuppress HIV RNA levels maximally (i.e., to <48 copies/mL) and to prevent further selection of resistance mutations. With the availability of multiple new ARVs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. In a patient with ongoing viremia and evidence of resistance, some drugs in a regimen (e.g., NNRTI, T-20, RAL) should be discontinued promptly to decrease the risk of selecting additional drug-resistance mutations in order to preserve the activity of these drug classes in future regimens. A new regimen should include at least two, and preferably three, fully active agents **(AII)**.

- ***Highly drug resistant HIV.*** There is a subset of patients who have experienced toxicity and/or developed resistance to all or most currently available regimens, and designing a regimen with two or three fully active drugs is not possible. Many of these patients received suboptimal ARV regimens (i.e., did not have access to more than one or two of the drugs at the time they became available) or have been unable to adhere to any regimen. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). There is no consensus on how to optimize the management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease **(BII)**. Even partial virologic suppression of HIV RNA >0.5 $\log_{10}$ copies/mL from baseline correlates with clinical benefits *[34]*. There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, reduces the risk of disease progression *[35]*. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL *[36-37]*. However, these potential benefits all must be balanced with the ongoing risk of accumulating additional resistance mutations.

  In general, adding a single, fully active ARV in a new regimen is **not** recommended because of the risk of rapid development of resistance **(BII)**. However, in patients with a high likelihood of clinical progression (e.g., CD4 cell count <100 cells/mm^3) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 cell counts have been associated with clinical benefits **(CI)**. Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., ARV activity) of using a single active drug in the heavily ART experienced patient is complicated, and consultation with an expert is advised.

  Patients with ongoing viremia and with an insufficient number of approved treatment options to construct a fully suppressive regimen may be candidates for research studies or expanded access programs, or single-patient access of investigational new drug(s) (IND), as specified in Food and Drug Administration (FDA) regulations: **http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm***)*.

  Discontinuing or briefly interrupting therapy in a patient with viremia may lead to a rapid increase in HIV RNA and a decrease in CD4 T-cell count and increases the risk of clinical progression *[38-39]*. Therefore, this strategy is **not** recommended **(AI)**. See **Discontinuation or Interruption of Antiretroviral Therapy**.

- ***Prior treatment and suspected drug resistance, now presenting to care in need of therapy with limited information (i.e., incomplete or absence of self-reported history, medical records, or previous resistance data).*** Every effort should be made to obtain medical records and prior drug-resistance testing results; however, this is not always possible. One strategy is to restart the most recent ARV regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen; another strategy is to start two or three drugs known to be active based on treatment history (e.g., MVC with R5 virus, RAL if no prior INSTI).

Immunologic Failure: Definition, Causes, and Management

Immunologic failure can be defined as the failure to achieve and maintain an adequate CD4 response despite virologic suppression. Increases in CD4 counts in ARV-naïve patients with initial ARV regimens are approximately 150 cells/mm^3 over the first year *[40]*. A CD4 count plateau may occur after 4–6 years of treatment with suppressed viremia *[41-45]*.

No accepted specific definition for immunologic failure exists, although some studies have focused on patients who fail to increase CD4 counts above a specific threshold (e.g., >350 or 500 cells/mm^3) over a specific period of time (e.g., 4–7 years). Others have focused on an inability to increase CD4 counts above pretherapy levels by a certain threshold (e.g., >50 or 100 cells/mm^3) over a given time period. The former criterion may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events *[46]*.

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 count >500 cells/mm^3 through 6 years of treatment was 42% in those starting treatment with a CD4 count <200 cells/mm^3, 66% in those starting with a CD4 count 200–350 cells/mm^3, and 85% in those starting with a CD4 count >350 cells/mm^3 *[41]*.

A persistently low CD4 count while on suppressive ART is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality *[47-48]*. For example, in the FIRST study *[49]*, a low CD4 count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.56 per 100 cells/mm^3 higher CD4 count). Similarly, a low CD4 count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, and renal disease and cancer. Other studies support these associations *[50-53]*.

Factors associated with poor CD4 T-cell response:
- CD4 count <200/mm^3 when starting ART
- Older age
- Coinfection (e.g., hepatitis C virus [HCV], HIV-2, human T-cell leukemia virus type 1 [HTLV-1], HTLV-2)
- Medications, both ARVs (e.g., ZDV *[54]*, TDF + didanosine [ddI] *[55-57]*) and other medications.
- Persistent immune activation
- Loss of regenerative potential of the immune system
- Other medical conditions

Assessment of Immunologic Failure. CD4 count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., cancer chemotherapy, interferon, prednisone, ZDV; combination of TDF and ddI), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure. No consensus exists on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 counts <200 cells/mm^3 because patients with higher CD4 counts have a lower risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the ARV regimen. Because ongoing immune activation occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit *[58]*. Others suggest changing the regimen to another regimen (e.g., from NNRTI-based to PI-based, INSTI-based, or CCR5 antagonist-based regimens), but this strategy has not shown clear benefit.

An immune-based therapy, interleukin-2, demonstrated CD4 count increases but no clinical benefit in two large randomized studies *[59]* and therefore is not recommended **(AI)**. Other immune-based therapies (e.g., gene therapies, growth hormone, cyclosporine, interleukin-7) are under investigation. Currently, immune-based therapies **should not** be used unless in the context of a clinical trial **(AIII)**.

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